EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the substantiation of a health claim related to caffeine and increased alertness pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to caffeine and increased alertness pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from SmithKline Beecham Limited, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of United Kingdom, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to caffeine and increased alertness. The food constituent, caffeine, which is the subject of the health claim, is sufficiently characterised. Increased alertness might be a beneficial physiological effect. A claim on caffeine and increased alertness, in the general adult population, for products containing at least 75 mg of caffeine per serving, has already been assessed by the Panel with a favourable outcome. In the present application, the applicant proposed that, in order to bear the claim, a product should contain at least 40 mg of caffeine per serving. In weighing the evidence, the Panel took into account that most studies which measured reaction time in various cognitive tasks found no effect of caffeine at doses < 75 mg. In the particular dose range between 40 and < 75 mg, no effect of caffeine was found on the majority of outcome measures of reaction time. The Panel notes that the majority of studies with caffeine doses of 75 mg or higher showed a significant reduction in measures of reaction time. On the basis of the evidence provided, the Panel reiterates its previous conclusion that, in order to bear the claim, a product should contain at least 75 mg caffeine per serving. The Panel concludes that a cause and effect relationship has not been established between the consumption of caffeine and increased alertness under the conditions of use proposed by the applicant.

KEY WORDS

caffeine, alertness, health claims

[1] On request from the Competent Authority of United Kingdom following an application by SmithKline Beecham Limited, Question No EFSA-Q-2013-00399, adopted on 5 February 2014.

[2] Panel members: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Sean (J.J.) Strain, Inge Tetens, Hendrik Van Loveren, Hans Verhagen and Peter Willatts for the preparatory work on this scientific opinion.

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SUMMARY

Following an application from SmithKline Beecham Limited, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of United Kingdom, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to caffeine and increased alertness.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.

The food constituent that is the subject of the health claim is caffeine, which is a well characterised food constituent and is measurable in foods by established methods. The Panel considers that caffeine is sufficiently characterised.

The claimed effect proposed by the applicant is "helps to increase alertness". The target population proposed by the applicant is "the general adult population". Alertness is a well defined construct and can be measured by validated psychometric cognitive tests (e.g. simple reaction time tasks, choice reaction time tasks, and other vigilance tasks measuring reaction time). The Panel considers that increased alertness might be a beneficial physiological effect.

A claim on caffeine and increased alertness, in the general adult population, for products containing at least 75 mg of caffeine per serving, has already been assessed by the Panel with a favourable outcome. The conclusion from the Panel was based on the evidence provided by consensus opinions/reports, and by the majority of the studies submitted for the scientific substantiation of the claim, which showed a consensus on the role of caffeine in increasing alertness as measured by reaction times in healthy individuals of both sexes, at doses of at least 75 mg.

In the present application, the applicant proposed that, in order to bear the claim, a product should contain a dose of caffeine of at least 40 mg per serving.

The applicant identified 18 human intervention studies, 15 human studies on bioavailability or mechanistic studies, one pooled analysis, and 12 non-human studies as being pertinent to the health claim.

Among the human intervention studies provided, one study did not allow the total dose of caffeine administered to be estimated, three studies did not report on measures of alertness as a cognitive construct and two studies were conducted in experimental conditions that are not representative of the conditions of use proposed by the applicant. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

Twelve randomised, double-blind placebo-controlled intervention studies investigated the effect of caffeine on alertness by using several measures of reaction time in regular caffeine consumers, who typically had abstained from caffeine for at least 12 hours. The Panel notes that most measures of simple reaction time tasks, choice reaction time, and reaction time in other vigilance tasks showed no effect of caffeine at doses < 75 mg.

The pooled analysis provided evaluated a selection of the evidence available and the selected studies were inappropriate to be pooled for analysis as they differed in design regarding time points, number of repetitions, and tests used to assess alertness. The Panel considers that such pooling is exploratory in nature and that it does not provide additional evidence for the scientific substantiation of the claim.

The Panel considers that no conclusions can be drawn from the human studies on bioavailability, the mechanistic studies and the non-human studies for the scientific substantiation of an effect of caffeine on alertness at the proposed condition of use (i.e. at least 40 mg per serving).

In weighing the evidence, the Panel took into account the fact that most studies found no effect of caffeine at doses < 75 mg on reaction time in various cognitive tasks (simple reaction time, choice reaction time and reaction time on other vigilance tasks). At the particular dose range between 40 and < 75 mg, no effect of caffeine was found on the majority of outcome measures of reaction time. The Panel notes that the majority of studies with caffeine doses of 75 mg or higher showed a significant reduction in measures of reaction time, irrespective of the type of tasks which were assessed. On the basis of the evidence provided, the Panel reiterates its previous conclusion that, in order to bear the claim, a product should contain at least 75 mg caffeine per serving.

The Panel concludes that a cause and effect relationship has not been established between the consumption of caffeine and increased alertness under the conditions of use proposed by the applicant.

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BACKGROUND

Regulation (EC) No 1924/2006[4] harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 10/07/2013.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.
- On 31/07/2013, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- On 19/08/2013, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 03/09/2013.
- On 21/11/2013, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The clock was stopped on 02/12/2013 and restarted on 17/12/2013, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 19/12/2013, EFSA received the requested information (which was made available to EFSA in electronic format on 16/12/2013).
- During its meeting on 05/02/2014, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to caffeine and increased alertness.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: caffeine and increased alertness.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of caffeine, a positive assessment of its safety, nor a decision on whether caffeine is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: SmithKline Beecham Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom.

The application includes a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006 for four unpublished studies (Haskell and Kennedy, 2011a, b; Rogers, 2011; Smith et al., 2011) and one unpublished pooled analysis (Lowe, 2012). For these studies and for some parts pertaining to the manufacturing process, the applicant also requested confidentiality.

Food/constituent as stated by the applicant

According to the applicant, the food constituent for which the claim is made is caffeine.

Health relationship as claimed by the applicant

According to the applicant, caffeine helps to increase alertness. According to the applicant, caffeine is rapidly absorbed and exerts neuroactive, alerting effects. These effects have been evaluated by employing psychometric instruments to assess changes in arousal (alertness, sleepiness, etc.) and by cognitive tests (simple reaction time, choice reaction time and further tests designed to measure rapid visual information processing). The cognitive tests are a direct measure of the claimed alerting effect.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "caffeine helps to increase alertness".

Specific conditions of use as proposed by the applicant

The applicant has proposed a dose of caffeine of at least 40 mg per serving in foods, food supplements and beverage products.

The target population proposed by the applicant is the general adult population.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is caffeine.

Caffeine is a natural compound present in coffee beans and tea leaves. Other sources include cocoa beans, kola nut, yerba mate, guarana berries and yaupon holly. Caffeine is a well characterised food constituent and is measurable in foods by established methods.

The Panel considers that the food constituent, caffeine, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is "helps to increase alertness". The target population proposed by the applicant is "the general adult population".

Alertness may relate to either a cognitive (i.e. behavioural) or an affective (i.e. subjective self-rating) construct. Cognitive alertness refers to a state of enhanced arousal and readiness to receive and process information and respond. Alertness is a well defined construct and can be measured by validated psychometric cognitive tests.

Reaction time (RT) is a measure of alertness as a cognitive construct. Cognitive tests used to measure RTs include simple reaction time tasks, choice reaction time tasks, and other vigilance tasks measuring RT (e.g. rapid information processing tasks, visual and auditory vigilance tasks).

The Panel considers that increased alertness might be a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

A claim on caffeine and increased alertness has already been assessed by the NDA Panel with a favourable outcome (EFSA NDA Panel, 2011). The target population was the general adult population. In weighing the evidence, the Panel took into account the fact that the evidence provided by consensus opinions/reports, and by the majority of the studies submitted for the scientific substantiation of the claim, showed that there was consensus on the role of caffeine in increasing alertness as measured by reaction times in healthy individuals of both sexes, at doses of at least 75 mg. Thus, the Panel considered that, in order to bear the claim, a product should contain at least 75 mg caffeine per serving.

In the present application, the applicant proposed that, in order to bear the claim, a product should contain a dose of caffeine of at least 40 mg per serving.

The applicant performed a literature search in PubMed using the search terms caffeine AND (alertness[All Fields] OR ("attention"[MeSH Terms] OR "attention"[All Fields]) OR processing[All Fields] OR ("cognition"[MeSH Terms] OR "cognition"[All Fields]) OR motor[All Fields]) AND ("humans"[MeSH Terms] AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Review[ptyp]) AND English[lang] AND ("adult"[MeSH Terms] OR "adolescent"[MeSH Terms])). The applicant included publications on caffeine and alertness in humans at doses < 60 mg. The applicant excluded publications on the effect of caffeine on alertness at doses ≥ 60 mg or ≥ 1 mg /kg body weight (b.w.). Publications on uncontrolled combinations of caffeine with other constituents (e.g. theanine, sugars) were excluded. The applicant described the literature search in PubMed that was performed to identify published non-human studies.

Through these literature searches the applicant identified a total of 37 publications as being pertinent to the health claim: 10 human intervention studies (Kuznicki and Turner, 1986; Lieberman et al., 1987a; Griffiths et al., 1990; Silverman and Griffiths, 1992; Mumford et al., 1994; Smith et al., 1999; Smit and Rogers, 2000; Van Dongen et al., 2001; Wyatt et al., 2004; Smith, 2009), 15 human studies on bioavailability or mechanistic studies (Marks and Kelly, 1973; Newton et al., 1981; Bonati et al., 1982; Blanchard and Sawers, 1983; Lelo et al., 1986; Nehlig et al., 1992; Liguori et al., 1997; Fredholm et al., 1999; Magkos and Kavouras, 2005; Specterman et al., 2005; Seng et al., 2009, 2010; Arnaud, 2011; Perera et al., 2011; Smith et al., 2013), and 12 non-human studies (Bunker and McWilliams, 1979; Arnaud, 1985; Schiffmann et al., 1991; Okada et al., 1996; Ledent et al., 1997; Wang and Lau, 1998; El Yacoubi et al., 2000; Fredholm et al., 2001; Yamato et al., 2002; Liu and Gao, 2007; Costa et al., 2008; Botton et al., 2010). The applicant also provided four human intervention studies (Rogers, 2011, unpublished; Smith et al., 2011, unpublished; Haskell and Kennedy, 2011a, 2011b, unpublished) and one pooled analysis (Lowe, 2012, unpublished), claimed proprietary, as being pertinent to the health claim.

The Panel considers that the scientific substantiation of this claim relates to doses of caffeine between 40 mg per serving (minimum effective dose proposed by the applicant) and 75 mg per serving (minimum effective dose proposed by EFSA). The Panel requested clarification from the applicant on the reason why the literature search was limited to studies conducted with doses of caffeine < 60 mg or < 1 mg/kg b.w. In its reply, the applicant identified four additional studies which used doses of caffeine < 75 mg or ≤ 1 mg/kg b.w. (Lieberman et al., 1987b; Rogers and Dernoncourt, 1998; Yeomans et al., 2002; Hewlett and Smith, 2007). In the paper by Hewlett and Smith (2007), subjects' body weight was not provided so the total caffeine dose cannot be estimated. The Panel considers that no conclusions can be drawn from this paper for the substantiation of the health claim.

Among the human intervention studies provided, three did not report on measures of alertness as a cognitive construct (Griffiths et al., 1990; Silverman and Griffiths, 1992; Mumford et al., 1994), but rather on subjective ratings of alertness, mood, or cognitive tasks for which reaction time was not assessed. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

Another intervention study (Wyatt et al., 2004) was conducted in subjects who had undergone a "forced circadian desynchrony paradigm" with an imposed wake-sleep and light-dark schedule of 42.85 hours (28.57-hour wake episodes and 14.28-hour sleep episodes) for 29 days. Caffeine was administered hourly during awakening at a dose of 0.3 mg/kg b.w. per hour. In the study by Van Dongen et al. (2001), subjects received repeated caffeine doses of 0.3 mg/kg b.w. per hour during an 88-hour period of wakefulness which included repeated two-hour naps. The Panel notes that the conditions of these experiments (i.e. subjects under extended artificial sleep deprivation conditions; high-frequency, repeated low-dose caffeine regimen) are not representative of the conditions of use proposed by the applicant. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

A total of 12 randomised, double-blind placebo-controlled (DBPC) intervention studies which assessed the effects of caffeine on reaction time (RT) were provided (Kuznicki and Turner, 1986; Lieberman et al., 1987a, 1987b; Rogers and Dernoncourt, 1998; Smith et al., 1999; Smit and Rogers, 2000; Yeomans et al., 2002; Smith, 2009; Rogers, 2011, unpublished; Smith et al., 2011, unpublished; Haskell and Kennedy, 2011a, unpublished; Haskell and Kennedy, 2011b, unpublished). The cognitive tests used to measure RTs were simple reaction time tasks, choice reaction time tasks, and other vigilance tasks measuring RT (e.g. rapid information processing tasks, visual and auditory vigilance tasks). Most studies included several measures of alertness. Overall, simple reaction time tasks were assessed in eight studies (Lieberman et al., 1987b; Lieberman et al., 1987a; Rogers and Dernoncourt, 1998; Smith et al., 1999; Smit and Rogers, 2000; Smith, 2009; Rogers, 2011, unpublished; Haskell and Kennedy, 2011b, unpublished), choice reaction time tasks were assessed in nine studies (Kuznicki and Turner, 1986; Lieberman et al., 1987b; Lieberman et al., 1987a; Smith et al., 1999; Smith, 2009; Rogers, 2011, unpublished; Smith et al., 2011, unpublished; Haskell and Kennedy, 2011a, unpublished; Haskell and Kennedy, 2011b, unpublished) and other vigilance tasks measuring RT were assessed in six studies (Smith et al., 1999; Smit and Rogers, 2000; Yeomans et al., 2002; Smith, 2009; Rogers, 2011, unpublished; Haskell and Kennedy, 2011b, unpublished).

Studies differed with respect to their design (parallel or crossover), number of subjects per study arm (10 to 44 subjects), and baseline characteristics of participants (age range 18-62 years; usual coffee consumption from 0 to 600 mg/day). Studies generally involved regular caffeine consumers who had typically abstained from caffeine for at least 12 hours. In most studies, the dose of caffeine administered was the same for all subjects in a given study arm (dose range: 10–64 mg), while in two studies the dose of caffeine was proportionate to the body weight of participants (1 mg/kg b.w.). All studies included caffeine doses < 75 mg in a single dose, provided in drinks, chewing gum or capsules. With respect to the performance assessment, studies differed with respect to the time between caffeine administration and RT testing and the number of assessment blocks (single or repeated). In the majority of the studies power calculations were not performed, the dropout rate was zero or very low, statistical adjustments for multiple outcome measures were not made and data were analysed on the population of completers only by analysis of variance (ANOVA) allowing for covariates.

3.1. Human intervention studies on simple reaction time tasks

Eight studies assessed the effect of caffeine on simple RT tasks. Of these, one (Lieberman et al., 1987b) reported a significant reduction in simple RT following caffeine consumption at a doses of 64 mg and one (Rogers and Dernoncourt, 1998) a significant main effect of caffeine on simple RT at 1 mg/kg b.w. (mean ± SE, 64.4 ± 2.0 kg b.w. in group of younger subjects and 68.9 ± 2.1 kg b.w. in

group of older subjects), with a significant caffeine × trial block interaction. No effect of caffeine was found in the first trial block, while significant effects were found in the two later trial blocks. There was no significant effect of age. In two studies the results were mixed: Rogers (2011, unpublished) observed a significant reduction in simple RT following caffeine consumption at a dose of 40 mg at t1, but not at t4 or when all time points were combined, whereas the effects at t2, t3 and t5 were not reported. Smit and Rogers (2000) observed a significant reduction in simple RT at doses of 12.5 mg and 50 mg, but not of 25 mg. The remaining five studies found no effect on simple RT tasks at doses of 10 mg (one outcome (Haskell and Kennedy, 2011b, unpublished)), 20 mg (one outcome (Haskell and Kennedy, 2011b, unpublished)), 32 mg (one outcome (Lieberman et al., 1987a)), 40 mg (three outcomes (Smith et al., 1999; Smith, 2009; Haskell and Kennedy, 2011b, unpublished)), and 64 mg (one outcome (Lieberman et al., 1987a)).

The Panel notes that most studies showed no effect of caffeine at doses < 75 mg on measures of simple RT tasks (two studies showed positive effects; two studies were inconsistent; five studies showed no effect). In the dose range of 40 to < 75 mg, positive effects of caffeine were reported at doses of 50 mg, 64 mg and 1 mg/kg b.w. caffeine (one outcome each), while no effect was observed at doses of 40 mg on three outcomes, and of 64 mg on one outcome. There was no indication that a no effect was obtained only in studies with small sample sizes and which may have been under-powered. Sample sizes ranged from 12 to 44 per arm, and the studies with the largest samples (> 40 per arm) all failed to find an effect of caffeine in the dose range of 40 to < 75 mg.

3.2. Human intervention studies on choice reaction time tasks

Of the nine studies which assessed the effect of caffeine on choice reaction time tasks, one found a significant effect of 32 mg and 64 mg caffeine on a four choice RT task (Lieberman et al., 1987a). Haskell and Kennedy (2011a, unpublished) found a significant effect of 40 mg caffeine on a two choice RT task when the results obtained at eight time points were combined. The Panel notes that a significant effect of caffeine compared with placebo was found at time points t2, t3, t4, t5 and t8, while no effect was found at time points t6 and t7. Smith et al. (1999) found a significant effect of 40 mg caffeine on a two choice focused attention choice RT task, and in a categoric search choice reaction time task. Rogers (2011, unpublished) reported a significant effect of 40 mg caffeine on a two choice RT task when results obtained at four time points were combined. The Panel notes that a significant effect of caffeine compared with placebo was not apparent at time points t1 and t4, while the results at time points t2 and t3 were not reported in the study. In the study by Smith et al. (2011, unpublished), no effect of 10 and 20 mg caffeine (analysed together) or 40 and 80 mg caffeine (analysed together) was found on a two choice RT test. Further analyses comparing the separate effects of 40 mg and 80 mg caffeine found no significant results at any time point. Smith (2009) found no effect of gum containing 40 mg caffeine compared with placebo gum on either a categoric search choice RT task or a focused attention choice RT task. The other three studies found no effect on choice RT tasks of 10 mg (one outcome (Haskell and Kennedy, 2011b, unpublished)), 20 mg (two outcomes (Kuznicki and Turner, 1986; Haskell and Kennedy, 2011b, unpublished)), 40 mg (two outcomes (Kuznicki and Turner, 1986; Haskell and Kennedy, 2011b, unpublished)), or 64 mg (one outcome (Lieberman et al., 1987b)),

The Panel notes that most studies showed no effect of caffeine at doses < 75 mg on measures of choice RT (three studies showed positive effects; one study was inconsistent; five studies showed no effect). In the dose range of 40 to < 75 mg, positive effects of caffeine were reported at doses of 40 mg on two outcomes and of 64 mg on one outcome, while no effect was observed at doses of 40 mg on five outcomes, and of 64 mg on one outcome. There was no indication that a no effect was obtained only in studies with small sample sizes and which may have been under-powered. Sample sizes ranged from 10 to 44 per arm, and among the studies with largest sample sizes (> 40 per arm), three reported no effect, while one reported a positive result in the dose range of 40 to < 75 mg.

3.3. Human intervention studies on other vigilance tasks

Of the six studies which reported on the effect of caffeine on RT in other vigilance tasks, Smith (2009) found a positive effect of 40 mg on RT in a repeated digits vigilance task. Yeomans et al. (2002) reported a significant effect of 1 mg/kg b.w. on RT (mean ± standard error (SE), 67.7 ± 2.2 kg b.w. in intervention group) on a rapid visual information processing task in caffeine deprived individuals. When an additional dose of 1 mg/kg b.w. was administered 60 min after the initial dose, no effect was observed compared with placebo. Haskell and Kennedy (2011b, unpublished) found a significant effect of 20 mg caffeine on RT in a digit vigilance task, but no effect at doses of 10 mg or 40 mg, and no effect on RT in a rapid visual information processing task at 10 mg, 20 mg, or 40 mg. Smith et al. (1999) found no effect of 40 mg caffeine on RT in a test for rapid visual information processing while Smit and Rogers (2000) found no effect on RT of doses of 12.5 mg, 25 mg and 50 mg caffeine in a rapid visual information processing task, and Rogers (2011, unpublished) found no effect of 40 mg caffeine on RT in a digit vigilance test.

The Panel notes that most studies showed no effect of caffeine at doses < 75 mg on RTs in other vigilance tasks (two studies showed positive effects; one study was inconsistent; three studies showed no effect). In the dose range 40 to < 75 mg, positive effects of caffeine on RTs in other vigilance tasks were reported at doses of 40 mg on one outcome and of 1 mg/kg b.w. on one outcome, while no effect was found with doses of 40 mg on four outcomes, and of 50 mg on one outcome. There was no indication that a no effect was obtained only in studies with small sample sizes and which may have been under-powered. Sample sizes ranged from 12 to 44 per arm, and among the studies with largest sample sizes (> 40 per arm), one reported a positive result, and one reported no effect in the dose range of 40 to < 75 mg.

3.4. Pooled analysis

The applicant provided an exploratory pooled analysis of the data from Rogers (2011, unpublished), Haskell and Kennedy (2011a, unpublished), Haskell and Kennedy (2011b, unpublished) and Smith et al. (2011, unpublished). The applicant indicated that these studies were selected because of their similar design and execution and the availability of individual data. As the doses and cognitive tests used differed among studies, the pooling was restricted to the doses (0 mg, 40 mg and 80 mg caffeine), which were common to the four studies, and to tests which were similar (simple RT tasks and choice RT tasks using various stimuli). In addition, the studies varied in the number of measurement time points (from five to eight time points), the number of repetitions of the tests (from one to seven repetitions), and the number of trials per test block. Thus, data from similar time points were pooled and the analysis was restricted to data for the first repetition of each assessment.

The Panel notes that this analysis evaluated a selection of the evidence available based on the availability of individual data from studies which were inappropriate to be pooled for analysis as they differed in design regarding time points, number of repetitions, and tests used to assess alertness. The Panel considers that such pooling is exploratory in nature and that it does not provide additional evidence for the scientific substantiation of the claim.

The Panel considers that no conclusions can be drawn from the human studies on bioavailability, the mechanistic studies and the non-human studies for the scientific substantiation of an effect of caffeine on alertness at the proposed condition of use (i.e. at least 40 mg per serving).

In weighing the evidence, the Panel took into account that most studies found no effect of caffeine at doses < 75 mg on RT in various cognitive tasks (simple RT, choice RT and RT on other vigilance tasks). In the particular dose range between 40 and < 75 mg, no effect of caffeine was found on the majority of outcome measures of RT. The Panel notes that the majority of studies with caffeine doses of 75 mg or higher showed a significant reduction in measures of RT, irrespective of the type of tasks which were assessed (EFSA NDA Panel, 2011). On the basis of the evidence provided, the Panel reiterates its previous conclusion that, in order to bear the claim, a product should contain at least 75 mg caffeine per serving.

The Panel concludes that a cause and effect relationship has not been established between the consumption of caffeine and increased alertness under the conditions of use proposed by the applicant.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent, caffeine, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is "helps to increase alertness". The target population proposed by the applicant is "the general adult population, male and female subjects aged 18 to 56 years old". Increased alertness might be a beneficial physiological effect
- A cause and effect relationship has not been established between the consumption of caffeine and increased alertness under the conditions of use proposed by the applicant.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on caffeine and increased alertness pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0393_UK). July 2013. Submitted by SmithKline Beecham Limited.

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ABBREVIATIONS

RT Reaction time